able 142. Demographics - Intent–to Treat Evaluable Population (continued)

TABLE 4.2.2

Demographic Details
Summary Statistics: Intent-to-Treat Population

	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		ALL PATIENTS	
	N	%	N	%	N	%
Sex						
MALE	12	48.0	11	44.0	23	46.0
FEMALE	13	52.0	14	56.0	27	54.0
Race						
WHITE	22	88.0	21	84.0	43	86.0
BLACK	2	8.0	0	0	2	4.0
ASIAN	1	4.0	2	8.0	3	6.0
OTHER	0	0	2	8.0	2	4.0

[Sponsor's Table 4.2.2. Item 8, Vol.1.87, p. 057]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variable

"The primary efficacy variable (ie time to onset of block suitable for surgery defined as time from completion of first injection until time of first akinesia score of at least 18) was based on the akinesia scores.

"Since the akinesia assessments were only made at set times following dosing ie the time to onset of satisfactory block could only take a limited number of values, the distributional assumption of normality was doubtful. As a result, time to onset of block suitable for surgery was compared between treatment groups using a Wilcoxon Test. Treatment medians have been presented together with an estimate of the difference and a non-parametric 95% confidence interval..."

"The median time to onset of block suitable for surgery was 10 min for both treatments (range: 4 to 25 min for levobupivacaine and 6 to 20 min for bupivacaine) for the 'intent-to-treat' population. The difference in time to onset of block suitable for surgery was estimated as 0 min (95% CI: -2 to 5 min) for both the 'intent-to-treat' and 'per- protocol' populations. This means that time to onset of block following dosing with levobupivacaine is unlikely to be greater than 5 min slower than that of bupivacaine. On average, there was no significant difference between the time to onset of block suitable for surgery (p=0.42 and p=0.41 for 'intent-to-treat' and 'per-protocol' respectively)."

Secondary Efficacy Variables:

<u>)tal Volume of Study Drug</u>

"Since the volume of anaesthetic given could only take a limited number of values ie in general the injections were a set volume, the distributional assumption of normality was doubtful. As a result, total volume of study drug was compared between treatment groups using a Wilcoxon Test. Treatment medians have been presented together with an estimate of the difference and a non-parametric 95% confidence interval ..."

"The median total volume of study drug was 10 ml (range: 5 to 15 ml) for both treatments for the 'intent-to-treat' population. The difference in total volume of study drug was estimated as 0 ml (95% CI: 0 to 2 ml). This means total volume of study drug is unlikely to be greater than 2 ml higher for levobupivacaine compared with bupivacaine. On average, there was no significant difference between the total volume of study drug (p=0.40 for 'intent-to-treat' analysis)."

[Item 8, Vol. 1.87, p. 041–043]

Pre-Operative Analgesia

Eighty percent (20/25) of patients had no pain, 16% (4/25) reported some pain and 4% (1/25) had much pain in both treatment groups."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. However, this possible covariate was not statistically significant (p=0.80) and therefore was not included in the model. The assumption of proportional odds was satisfied (p=1 .00). The odds ratio levobupivacaine/bupivacaine) was 1.00 (95% CI: 0.25, 3.98). This means that there is no evidence of a difference in the odds of having a lower pain assessment between the 2 treatment groups. The Wald Statistic for a treatment difference
was not statistically significant (p=1.00)."

Post-Operative Analgesia

"Eight percent (2/25) of levobupivacaine patients had some pain compared with 4% (1/25) in the bupivacaine group. No patients in either treatment group reported much pain."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. However, this possible covariate was not statistically significant (p=0.16) and therefore was not included in the model. The assumption of proportional odds was automatically satisfied since the response variable took only 2 different values. The odds ratio levobupivacaine/bupivacaine) was 0.48 (95% CI: 0.04, 5.65). This means that the odds of having no pain are 0.48 times higher in the levobupivacaine group compared with bupivacaine ie the odds of having some pain are almost 2 times higher in the levobupivacaine group compared with bupivacaine. The Wald Statistic for a treatment difference was not statistically significant (p=0.56)."

Operating Conditions

Sixty eight percent (17/25) of levobupivacaine patients had excellent operating conditions compared with 56% (14/25) in the bupivacaine group. Satisfactory operating conditions were reported for 28% (7/25) of levobupivacaine patients compared with 44% (11/25) of bupivacaine
patients. Poor operating conditions were reported for one patient (4%) in the levobupivacaine group."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. However, this possible covariate was not statistically significant (p=0.21) and therefore was not included in the model. The assumption of proportional odds was satisfied (p=0.19). The odds ratio (levobupivacaine/bupivacaine) was 1.54 (95% CI: 0.49, 4.84). This means that the odds of having more favourable operating conditions are 1.54 times higher in the levobupivacaine group compared with bupivacaine. The Wald Statistic for a treatment difference was not statistically significant (p=0.46)."

[Item 8, Vol. 1.87, p. 043 – 044]

Table 159. Analysis of Primary Outcome Measurement

TABLE 8.4

Akinesia Score for Each Muscle at First Report of Satisfactory Block
Summary Statistics: Intent-to-Treat Population

Muscle	Akinesia Score									
	0.75% LEVOBUPIVACAINE					0.75% BUPIVACAINE				
	MEAN	SD	MIN	MAX	N	MEAN	SD	MIN	MAX	N
Superior Rectus	2.8	0.4	2	3	25	2.8	0.6	2	4	25
Inferior Rectus	3.2	0.6	2	4	25	3.5	0.6	2	4	25
Medial Rectus	3.8	0.5	2	4	25	3.8	0.4	3	4	25
Lateral Rectus	3.6	0.6	2	4	25	3.6	0.5	3	4	25
Orbicularis Oculi	3.1	0.4	2	4	25	2.9	0.4	2	4	25
Levator Palp Superioris	3.0	0.6	2	4	25	2.8	0.6	2	4	25

[Sponsor's Table 8.4, Item 8, Vol. 1.87, p. 071]

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ON ORIGINAL

Table 160. Analysis of Secondary Outcome Measurement

TABLE 9.2

.Total Volume of Study Drug
Summary Statistics: Intent-to-Treat Population

	Total Volume of Study Drug (ml)	
	0.75% LEVOBUPIVACAINE	0.75% BUPIVACAINE
MEAN	10.9	10.1
SD	2.6	2.7
MEDIAN	10.0	10.0
MIN	5	5
MAX	15	15
N	25	25

[Sponsor's Table 9.2, Item 8, Vol. 1.87, p.173]

Table 161. Analysis of Secondary Outcome Measurement

TABLE 10

Pre-operative Analgesia
Summary Statistics: Intent-to-Treat Population

Pre-operative Analgesia	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE	
	N	%	N	%
NO PAIN	20	80.0	20	80.0
SOME PAIN	4	16.0	4	16.0
MUCH PAIN	1	4.0	1	4.0
ALL PATIENTS	25	100.0	25	100.0

[Sponsor's Tables 10, Item 8. Vol. 1.87, p. 174]

Table 162. Analysis of Secondary Outcome Measurement

TABLE 11

Post-operative Analgesia
Summary Statistics: Intent-to-Treat Population

Post-operative Analgesia	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		ALL PATIENTS	
	N	%	N	%	N	%
NO PAIN	23	92.0	24	96.0	47	94.0
SOME PAIN	2	8.0	1	4.0	3	6.0

[Sponsor's Tables 11, Item 8. Vol. 1.87, p. 175]

Table 163. Analysis of Secondary Outcome Measurement

TABLE 12

Operating Conditions
Summary Statistics: Intent-to-Treat Population

Operating Conditions	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		ALL PATIENTS	
	N	%	N	%	N	%
EXCELLENT	17	68.0	14	56.0	31	62.0
SATISFACTORY	7	28.0	11	44.0	18	36.0
POOR	1	4.0	0	0	1	2.0

[Sponsor's Table 12, Item 8, Vol. 1.87, p. 176]

REVIEWER'S EFFICACY DISCUSSION

The primary measure of efficacy was onset of block adequate for surgery based upon akinesia scores. No significant difference was found (difference between the two groups estimated at 0 min ; 95%CI: -2 to 5 min) between levobupivacaine and bupivacaine in time to onset of block suitable for surgery. Additionally, there was no significant difference between the total volume of study drug required to achieve block adequate for surgery for the two treatment groups.

There was a difference in the number of patients complaining of pain immediately following surgery, however. The sponsor reports that the odds of having some pain were almost 2 times higher in the levobupivacaine group compared with the bupivacaine group. Additionally, the odds of having more favorable operating conditions was reported to be 1.54 times higher in the bupivacaine group. These were found to be of no statistical significance, however.

The clinical data has demonstrated that levobupivacaine is effective when administered as a peribulbar block for ophthalmic anterior segment surgery. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for ophthalmic anterior segment surgery. Additionally, levobupivacaine has been shown to have a similar time to onset as bupivacaine.

STUDY # 030737

PROTOCOL SYNOPSIS:

Title:	"A Study to Compare the Efficacy and Safety of 0.75% Bupivacaine with 0.75% Levobupivacaine in Peribulbar Block for Ophthalmic Anterior Segment Surgery"
Primary Objective:	"To compare the efficacy of 0.75% levobupivacaine with 0.75% bupivacaine in peribulbar block."
Secondary Objective:	"The relative safety profiles of the 2 different formulations were considered."

Study Design:

The study is designed as a single center, randomized, double blind, parallel group comparative study of the efficacy, and safety of 0.75% levobupivacaine with 0.75% racemic bupivacaine in peribulbar block for ophthalmic anterior segment surgery. The protocol calls for two groups of thirty patients to each be randomly assigned to one of two treatment arms.

Group I	0.75% levobupivacaine
Group II	0.75% bupivacaine

Eligible patients were ASA Class I or II males ≥ 18 years of age, consenting to receive peribulbar block for ophthalmic anterior segment surgery. Patients had no prior history of systemic illness, drug or alcohol abuse within the previous 6 months, participation in this or some other clinical trial in previous month, severe visual handicap in the other eye. Women of childbearing potential were neither pregnant nor lactating.

Eligible patients underwent a brief screening phase followed by a 1:1 randomization (30 patients per group) to receive either 0.75% levobupivacaine or 0.75% bupivacaine via peribulbar block. All patients received cyclopentolate and phenylephrine eye drops to dilate the pupil (except patients 008,014, 027, 028, 031, 036, 040, 053, 054, and 055) followed by benoxinate drops to provide conjunctival anesthesia. After 2 min, with the patient in primary gaze position, 5 ml of the randomized drug was inferio-temporally above the orbital rim (Time 0). If needed an additional 5-ml of study drug could be injected 10 min later medially between the caruncle and medial canthus. However, at no time was this second injection required.

The primary measure of efficacy was defined as the time to anesthesia suitable for surgery, i.e., total akinesia score of at least 12 and at least 2 for the orbicularis oculi muscle. The akinesia scoring system was used to assess degree of anesthesia for the 4 recti muscle, and levator palpebrae superioris according to the following scale:

Akinesia Scoring System:

0 = full movement
1 = almost full movement
2 = partial movement
3 = almost no movement
4= no movement

The orbicularis oculi muscle was scored according to the following scale:

Orbicularis Oculi Akinesia Scoring System

0 = assessor unable to manually force the eye open
1 = good closure but can be overcome
2 = closure of eye but is easily overcome
3 = eye is just closing
4 = patient is unable to close eye

Assessments were made at pre-dose, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min following the first injection or until satisfactory block was obtained. This assessment was repeated at the follow-up visit 24 hours post-discharge in order to confirm regression (score of less 0) of the block.

The patients assessed peri-operative analgesia immediately after the administration of the block and immediately after surgery using the following 3 point scale:

Pain Scoring System

0 = No pain
1 = Some pain
2 = Much pain

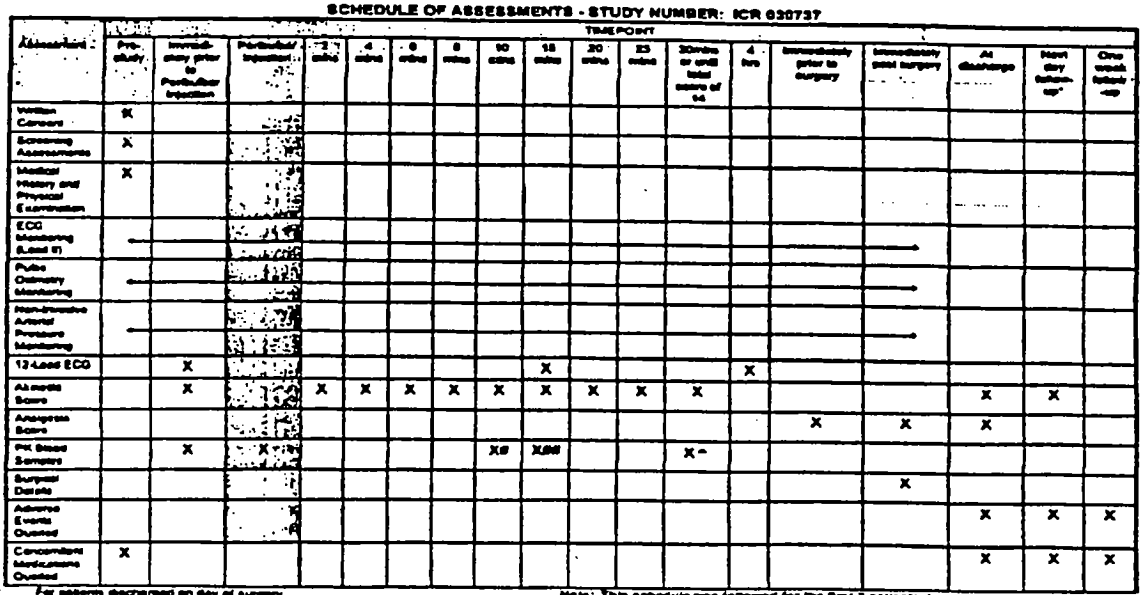
The surgeon rated the operating conditions according to the amount of eye movement present during surgery, where 0 = no movement, 1 = minimal movement, and 2 = excessive movement.

Additionally, patients were given a diary to record any post-operative analgesia experience when they left the hospital. These cards were collected at the next day follow-up visit.
Blood samples were taken to measure levobupivacaine and bupivacaine concentrations for all patients at the following times: pre-dose, after the first injection (Time 0), 10 min (before the second injection), 15 min, 30 min, 1 hour, and 2 hour post-dose. For the first three patients a 45 min sample was also taken; however, this was not uniformly measured in all patients - at the request of the surgeons, the 45 min sample was omitted for subsequent patients so as not to interfere with their surgery.

Where possible, samples were also taken at 4, 6, 8, 10 and 12 hours post-dose. At the request of the surgeons, samples at 10 and 12 hours were not taken for any patients; after the first 3 patients were completed, the requirement for these samples was omitted.

Table 164. Schedule of Assessments

SCHEDULE OF ASSESSMENTS - STUDY NUMBER: ICR 030737



[Sponsor's Table I, "Schedule of Assessments", Item 8, Vol. 1.88, p. 015]

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STATISTICAL ANALYSIS

"The primary efficacy endpoint was defined as the time to onset of block suitable for surgery (i.e., time from completion of first injection until time of first total general akinesia score of at least 12 and a score of at least 2 for the orbicularis oculi muscle."

"The confirmatory efficacy analysis was to focus on the question of whether levobupivacaine was significantly better than bupivacaine with respect to clinical efficacy."

The statistical hypotheses behind this trial were as follows:

H_o: The mean difference in the time to anaesthetic suitable for surgery between the treatment groups is less than 5 min"

H_1: The mean difference in the time to anaesthetic suitable for surgery between the treatment groups is more than 5 min"

"The primary response variable was to be analysed using analysis of variance (ANOVA) with a term for treatment. Using the error variance from the ANOVA, comparison of the treatment LS Means (ie means adjusted for any imbalance in the design) were to be made using a Student's 't'-test. Estimates of treatment difference and associated 95% confidence interval were to be calculated."

"The residuals from this analysis were to be submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption was to entail a re-analysis using an appropriate alternative transformation of the data eg log transformation. Furthermore, following examination of these data, non-parametric methods were to be used if the above methods were not considered appropriate ie Wilcoxon Test and confidence intervals based on the Mann-Whitney test Statistic."

[Item 8., Vol. 1.88 p. 033 – 034]

Secondary Efficacy Variable:

"The secondary efficacy response variables were defined as follows:

(4) Total volume of study anaesthetic required to achieve adequate block,
(5) Pre-operative analgesia (ie following administration of block) using a 3 point rating scale (0 = no pain, 1 = some pain, 2 = much pain),
(6) Post-operative analgesia (ie immediately after surgery) using a 3 point rating scale (0 = no pain, 1 = some pain, 2 = much pain),
(7) Analgesia at discharge using a 3 point rating scale (0 = no pain, 1 = some pain, 2 = much pain),
(5) Operating conditions using a 3 point rating scale (0 = excellent, 1 = satisfactory, 2 = poor),
(6) Time from completion of first injection to first requirement for post-operative analgesia."

"Total volume of anaesthetic was to be analysed in an identical way to the primary endpoint (ie ANOVA) using the 'intent-to-treat' and per-protocol populations."

"Pre-operative, post-operative analgesia, analgesia at discharge, and operating conditions were to be analysed using a logit model including a term for treatment using the 'intent-to- treat' population only. The interval between achievement of suitable block until the start of surgery was to be considered as a covariate in these analyses. The significance level of the treatment effect was to be investigated using the Wald statistic. The odds ratio of the treatment difference and the associated 95% confidence interval were to be calculated. The logit model assumes proportional odds across the categories of the response variable. The validity of this assumption was to be tested using the score test statistic for goodness–of-fit. If this assumption was clearly not satisfied, non-parametric methods were to be used."

"The time until first requirement of post-operative analgesia was to be presented using Kaplan-Meier survival curves. Patients not requiring analgesia were to be included in the analysis as censored observation. Comparisons between the 2 treatment groups was to be performed using a Wilcoxon test."

[Item 8, Vol. 1.88, p. 035-036]

PROTOCOL AMENDMENT:

The following amendment was dated 5/20/97. It consisted of following changes:

1. Pharmacokinetic Sampling
   - Only the first 20 patients were sampled at the following times: pre-dose, after the first injection , 10, 15, 30 min, 1h, and 2h post dose - previously all patients were sampled at those times.
   - The following sampling times have been eliminated: 45 min, 10h and 12h after the first injection.
   - The centrifugation rate was 1500 G not 500G –editorial error
2. Study Procedures
   - The sponsor has eliminated the 12 – lead ECG and replaced it with simply monitoring lead II. ECG monitoring still occurred immediately prior to study drug administration, as well as at 15 min and 4 hours after Time 0.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 60 patients randomized, all 60 100%) were considered eligible for the intent-to-treat population and per-protocol populations.

Patients 001, 002, 003, 010, 043, and 045 did not receive safety monitoring i.e., continuous ECG, arterial pressure and pulse oximetry, prior to dose administration. Patient 004's safety monitoring was finished 2 minutes before surgery was completed. These patients, despite being considered to be protocol deviators, were deemed evaluable for the per-protocol population.

Additionally, patients 008, 014, 027, 028, 031, 036, 040, 053, 054, and 055 did not receive mydriatic drops prior to surgery as the use of these drops was a inappropriate for the type of surgery they were undergoing – simple trabeculectomy. These patients were deemed evaluable for the per-protocol population.

Table 165. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			60 (100) Randomized
Excluded from Safety Population:			
None			60 (100) Safety Population
Excluded from Intent-to-Treat:			
None			60 (100) Intent-to-Treat
Excluded from Per-Protocol:			
None			60 (100) Per-Protocol
0 (0%) Total Withdrawal			60 (100%) Total Completed

Table 166. Patient Disposition

TABLE 1

Patient Recruitment and Exclusions from Populations
Summary Statistics: All Patients

	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		ALL PATIENTS	
	N	%	N	%	N	%
Patients Recruited onto Study	30	100.0	30	100.0	60	100.0
Patients Dosed	30	100.0	30	100.0	60	100.0
Safety Population	30	100.0	30	100.0	60	100.0
Intent-to-Treat Population	30	100.0	30	100.0	60	100.0
Per-Protocol Population	30	100.0	30	100.0	60	100.0
Early Withdrawals	0	0	0	0	0	0

[Sponsor's Table 1, Item 8, Vol. 1. 88 p. 065]

Demographics

The following table summarizes the demographic characteristics of the two treatment groups:

Table 167. Demographics - All Patients

TABLE 2.1

Demographics
Summary Statistics: All Patients

		0.75% LEVOBUPIVACAINE	0.75% BUPIVACAINE	ALL PATIENTS
Age (Years)	Mean	76.6	77.6	77.1
	SD	8.1	8.7	8.3
	Min	60	56	56
	Max	90	90	90
	N	30	30	60
Height (cm)	Mean	164.6	163.8	164.2
	SD	8.3	9.8	9.0
	Min	152	142	142
	Max	180	183	183
	N	30	30	60
Weight (kg)	Mean	74.10	65.40	69.75
	SD	12.94	12.97	13.57
	Min	50.6	45.0	45.0
	Max	106.0	99.8	106.0
	N	30	30	60

[Sponsor's Table 2.1, Item 8, Vol.1.88, p. 066]

Table 150. Demographics – All Patients (continued)

TABLE 2.2

Demographics.
Summary Statistics: All Patients

	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE		ALL PATIENTS	
	N	%	N	%	N	%
Sex						
MALE	10	33.3	10	33.3	20	33.3
FEMALE	20	66.7	20	66.7	40	66.7
Race						
WHITE	30	100.0	30	100.0	60	100.0

[Sponsor's Table 2.2., Item 8, Vol. 1.88, p. 067]

Study Population

"A total of 60 patients completed the study, of which 40 were female and 20 were male, with a mean age for all patients of 77.1 years (range 56-90 years, SD = 8.3) were recruited. The whole study group had a mean height of 164.2 cm (range 142-183 cm, SD = 9.0) and a mean weight of 69.75 kg (range 45.0-106.0 kg, SD 13.57)."

"Thirty patients received levobupivacaine and 30 patients received bupivacaine. The levobupivacaine group had a mean age of 76.6 years (range 60-90 years, SD = 8.1), a mean height of 164.6 cm (range 152- 180cm, SD 8.3) and a mean weight of 74.10 kg (range 50.6-106.0 kg, SD = 12.94). The bupivacaine group had a mean age of 77.6 years (range 56-90 years, SD = 8.7), a mean height of 163.8 cm (range 142-183 cm, SD = 9.8) and a mean weight of 65.40 kg (range 45.0-99.8 kg, SD = 12.97)."

"The incidence of the various disease types (except for endocrine, nutritional, metabolic, immunity) was spread evenly amongst the treatment groups. The most commonly reported medical conditions were of the nervous system and sense organs, present in 100.0% of patients, of the circulatory system, present in 53.3% of patients, and of the musculoskeletal system and connective tissue and the digestive system, each present in 26.7% of patients."

"In addition, 15 of the 60 patients (25%) had undergone previous operations on their eyes."

[Item 8, Vol., 1.88, p. 042 –045]

A total of 51 patients, 24 in the levobupivacaine group and 27 in the bupivacaine group, took concomitant medication unrelated to surgery prior to the first peribulbar injection."

"Medications for cardiovascular conditions were taken by 46.7% of patients, mainly for the control of hypertension or angina. Medications relating to control of conditions associated with sensory organs were taken by 35.0% of patients, most commonly for glaucoma or dry eyes. Central nervous system medications were also taken by 26.7% of patients predominantly for anxiety' or insomnia."

"In addition, medications associated with the alimentary tract and metabolism were taken by 25.0% of patients, most commonly for hiatus hernia or diabetes. Medications for blood and blood forming organs were taken by 24.3% of patients, mainly for the control of coronary artery disease or vascular disease."

"Medications associated with sensory organs were the most common concomitant medications and were taken by 100.0% of patients. This represented the medications given for antibiotic, anti-inflammatory and mydriatic action post-study medication."

"In addition, 18.3% of patients received medications for various indications associated with the central nervous system but most commonly for eye pain."

[Item 8, Vol., 1.88, p. 046 –047]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variable

"Since the akinesia assessments were only made at set times following dosing ie the time to onset of satisfactory block could only take a limited number of values, the distributional assumption of normality was doubtful. As a result, time to onset of block suitable for surgery was compared using a logit model."

"Sixty three percent (19/30) of the Levobupivacaine patients had a time to adequate block of 2 min compared with 77% (23/30) of the Bupivacaine patients. Thirty three percent (10/30) of the Levobupivacaine patients had a time to adequate block of 4 min compared with 23% (7/30) of the Bupivacaine patients. Three percent (1/30) of the Levobupivacaine patients had a time to adequate block of 6 min."

"The assumption of proportional odds was satisfied (p=0.46). The odds ratio (Levobupivacaine/Bupivacaine) was 0.51(95% CI: 0.16, 1.56). This means that the odds of having a shorter time to adequate block are 0.51 times higher in the Levobupivacaine group compared with the Bupivacaine group ie the odds of having a longer time to adequate block almost 2 times higher in the Levobupivacaine group compared with the Bupivacaine group. The Wald Statistic for a treatment difference was not statistically significant (p=0.24)."

[Item 8, Vol. 1.88, p. 049 – 050]

Table 168. Analysis of Primary Efficacy Variable – Time to Onset of Satisfactory Block

TABLE 6.2

Time to Satisfactory Block (minutes)
Summary Statistics: Intent-to-Treat Population

	Time to Satisfactory Block (min)	
	0.75% LEVOBUPIVACAINE	0.75% BUPIVACAINE
MEAN	2.8	2.5
SD	1.1	0.9
MEDIAN	2.0	2.0
MIN	2	2
MAX	6	4
N	30	30

[Sponsor's Table 6.2, Item 8 Vol. 1.88, p. 076]

Secondary Efficacy Variables:

Total Volume of Study Drug

"Total volume of study drug was equal to 5 ml for all patients and therefore no statistical analysis was performed for this variable."

Pre-Operative Analgesia

"Seventy three percent (23/30) of patients had no pain and 23% (7/30) reported some pain in both treatment groups. No patients in either treatment group reported much pain."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. However, this possible covariate was not statistically significant (p=0.46) and therefore was not included in the model. The assumption of proportional odds was automatically satisfied since the response variable only took 2 different values. The odds ratio (Levobupivacaine/Bupivacaine) was 1.00 (95% CI: 0.32, 3.31). This means that there is no evidence of a difference in the odds of having a lower pain assessment between the 2 treatment groups. The Wald Statistic for a treatment difference was not statistically significant (p=1.00)."

[Item 8, Vol. 1.88, p. 050-051]

Table 169. Analysis of Secondary Variable

Total Volume of Study Drug

TABLE 7

Total Volume of Study Drug
Summary Statistics: Intent-to-Treat Population

	Total Volume of Study Drug (ml)	
	0.75% LEVOBUPIVACAINE	0.75% BUPIVACAINE
MEAN	5.0	5.0
SD	0.0	0.0
MEDIAN	5.0	5.0
MIN	5	5
MAX	5	5
N	30	30

Sponsor's Table 7, Item 8, Vol. 1.88, p. 080]

Post-Operative Analgesia

"One hundred percent (30/30) of Levobupivacaine patients had no pain compared with 97% (29/30) in the Bupivacaine group. Three percent (1/30) of Bupivacaine patients had some pain compared with no patients in the levobupivacaine group. No patients in either treatment group reported much pain."

"As there were no Levobupivacaine patients with some pain, the odds ratio between the 2 treatment groups was undefined (a division by zero would have been necessary) and no logit model could be applied. Hence Fisher's Exact test was applied. The treatment difference was not statistically significant (p=1.00)."

Analgesia at Discharge

"Ninety-seven percent (29/30) of patients had no pain and 3% (1/30) reported some pain in both treatment groups. No patients in either treatment group reported much pain."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. However, this possible covariate was not statistically significant (p=0.25) and therefore was not included in the model. The assumption of proportional odds was automatically satisfied as the response variable only took 2 different values. The odds ratio (Levobupivacaine/Bupivacaine) was 1.00 (95% CI: 0.06, 16.76). This means that there is no evidence of a difference in the odds of having a lower pain assessment between the 2 treatment groups. The Wald Statistic for a treatment difference was not statistically significant (p=1.00)."

[Item 8, Vol. 1.88, p. 051 –052]

Table 170. Analysis of Secondary Efficacy Variable – Pre-operative Analgesia

TABLE 8

Pre-operative Analgesia
Summary Statistics: Intent-to-Treat Population

Pre-operative Analgesia	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE	
	N	%	N	%
NO PAIN	23	76.7	23	76.7
SOME PAIN	7	23.3	7	23.3

Table 171. Analysis of Secondary Efficacy Variable – Post – operative Analgesia

TABLE 9

Post-operative Analgesia
Summary Statistics: Intent-to-Treat Population

Post-operative Analgesia	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE	
	N	%	N	%
NO PAIN	30	100.0	29	96.7
SOME PAIN	0	0	1	3.3

[Sponsor's Tables 8 and 9 , Item 8, Vol. 1.88, p. 081 and 082]

Operating Conditions

"Eighty seven percent (26/30) of Levobupivacaine patients had excellent operating conditions compared with 90% (27/30) in the Bupivacaine group. Satisfactory operating conditions were reported for 3% (1/30) of Levobupivacaine patients compared with 10% (3/30) of Bupivacaine patients. Ten percent (3/30) in the Levobupivacaine group reported poor operating conditions."

"The time from achievement of suitable block until the start of surgery was considered as a covariate in the model. This possible covariate was statistically significant (p=0.03) and therefore was included in the model. The assumption of proportional odds was satisfied (p=0.11). The odds ratio (Levobupivacaine/Bupivacaine) was 0.58 (95% CI: 0.11, 3.06). This means that the odds of having more favourable operating conditions are 0.58 times higher in the Levobupivacaine group compared with Bupivacaine (ie the odds of having less favourable operating conditions are 1.72 times higher in the Levobupivacaine group compared with the bupivacaine group). The Wald Statistic for a treatment difference was not statistically significant (p=0.52)."

Time from Completion of First Injection to First Post-Operative Analgesia

"The Wilcoxon test did not reveal any significant treatment differences (p=0.63)."

Please note the statistical review for analyses of additional measurements.

[...em 8, Vol. 1.88, p. 052 – 053]

Table 172. Analysis of Secondary Outcome Measurement

Operating Conditions

TABLE 11

Operating Conditions
Summary Statistics: Intent-to-Treat Population

Operating Conditions	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE	
	N	%	N	%
EXCELLENT	26	86.7	27	90.0
SATISFACTORY	1	3.3	3	10.0
POOR	3	10.0	0	0

[Sponsor's Table 11, Item 8, Vol. 1.88, p. 084]

Table 173. Analysis of Secondary Outcome Measurement – Post-Operative Analgesia Requirement

TABLE 12

Patients Requiring Post Operative Analgesia
Statistical Analysis: Intent-to-Treat Population

	0.75% LEVOBUPIVACAINE		0.75% BUPIVACAINE	
	N	%	N	%
YES	6	20.0	5	16.7
NO	24	80.0	25	83.3
ALL PATIENTS	30	100.0	30	100.0

[Sponsor's Tables 12, Item 8, Vol. 1.88, p.085]

REVIEWER'S EFFICACY DISCUSSION

"The primary measure of efficacy was the time to onset of anesthetic block adequate for surgery based on akinesia scores. The sponsor reports that, "the odds of a longer time to adequate anaesthetic block were almost 2 times higher in the levobupivacaine group compared with the bupivacaine group. However, the treatment difference was not statistically significant."

There was no difference between, (1) the total volume of study drug required to achieve anesthetic block adequate for surgery, (2) pain experienced following study drug administration, or 3) pain reported at discharge between the 2 groups.

However, time from achievement of suitable block until the start of surgery (a covariate in the model) was statistically significant (p=0.03) in favor of bupivacaine, i.e., the odds of having more favorable operating conditions was reported to be 0.58 times higher in the levobupivacaine group than in the bupivacaine group.

None of the levobupivacaine patients reported pain immediately following surgery, however.

The clinical data shows that despite levobupivacaine demonstrating almost twice as long to achieve an adequate anesthetic block compared with the bupivacaine, the treatment difference was not statistically significant (p=0.24). However, levobupivacaine is effective when administered as a peribulbar block for ophthalmic surgery based upon the clear evidence that patients experienced some level of analgesia sufficient for ophthalmic anterior segment surgery..

STUDY # 030700

PROTOCOL SYNOPSIS:

Title: "A Study to Compare the Efficacy and Safety of Levobupivacaine (0.75%), Lignocaine (2% with adrenaline) and Placebo as Post-operative Pain Relief in Patients Undergoing Unilateral or Bilateral Impacted Third Molar Extractions"

Primary Objective: "To compare the efficacy of 0.75% levobupivacaine with 2% lignocaine (with adrenaline) and placebo as post-operative pain relief in patients who underwent unilateral or bilateral impacted mandibular 3rd molar extractions."

Secondary Objective: "To compare the safety of the study medication."

[Item 8, Vol. 1.90, p. 016]

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ON ORIGINAL

The primary measure of efficacy was defined as the proportion of patients requiring rescue analgesia within 2 urs after the completion of surgery.

Secondary measures were as follows:

1. Time to the first requirement for analgesia
2. The proportion of patients requiring rescue analgesia over a period of 48 hours
3. The maximum pain score recorded on the VAS over the 2 hour period, post-surgery
4. The time at which the maximum pain score was documented
5. The proportion of patients whose sensory block wore off within 2 h post-surgery
6. The pain score as recorded on VAS at 8 hour post completion of surgery
7. The proportion of patients complaining of disturbed sleep due to pain at 10a.m. on the morning following surgery.
8. The pain score as recorded on VAS at 24 hours post completion of surgery.

STATISTICAL ANALYSIS

"The primary analysis population for efficacy in this study is the 'intent-to- treat' population. Additionally, the analysis of the primary efficacy variable was also performed using the 'per-protocol' population to confirm results obtained in the 'intent-to-treat' analysis."
"All tests for a difference between study medications were performed at the 5% significance level and the resulting p-values were two-sided. Differences between the treatment groups were estimated as 'levobupivacaine - lignocaine with adrenaline and levobupivacaine placebo. The differences were presented together with 95% confidence intervals."

Primary Measure of Efficacy

"The primary efficacy measure was the proportion of patients requiring rescue analgesia within 2 h of surgery. Patients that withdrew from the study within 2 h of surgery but without taking rescue analgesia had the primary efficacy variable set to 'rescue medication taken'. Patients where no information had been recorded whether they took rescue medication or not were handled in the same way. In both cases this followed a conservative approach since it could not be ruled out that these patients have taken rescue medication within the 2 h of surgery."
"The following hypothesis was tested:

H_0: The proportion of patients requiring rescue analgesia in the levobupivacaine treatment group is equal to the proportion of patients requiring rescue analgesia in the lignocaine group, and the proportion of patients requiring rescue analgesia in the levobupivacaine treatment group is also equal to the proportion of patients requiring rescue analgesia in the placebo treatment group.

H_A: The proportion of patients requiring rescue analgesia in the levobupivacaine treatment group is different from the proportion of patients requiring rescue analgesia in the lignocaine with adrenaline group, or the proportion of patients requiring rescue analgesia in the levobupivacaine treatment group is different from the proportion of patients requiring rescue analgesia in the placebo treatment group."

"For both the 'intent-to-treat' (primary analysis) and 'per-protocol' (secondary analysis) populations the following statistical analyses were performed:

[Item 8, Vol. 1.90, p. 031 –033]

Secondary Measures of Efficacy

The secondary efficacy response variables were defined as follows:

(1) The time of first requirement for rescue analgesia. Patients not requiring rescue medication were censored at the time of withdrawal from the study or at 48 h if they completed the study.

(2) The proportion of patients requiring rescue analgesia within 48 h of surgery. Patients that were withdrawn from the study without taking rescue analgesia had this variable set to 'rescue medication taken'. Patients where no information has been recorded whether they took rescue medication or not were handled in the same way.

(3) The maximum VAS pain score recorded over the 2 h period after surgery.

(4) The time to maximum VAS pain score over the 2 h period after surgery. Actual times were used to calculate this variable rather than target times. If the time to maximum VAS pain score was not uniquely defined, then the earliest time was utilised.

(5) The VAS pain score recorded 8 h after surgery. Patients that were withdrawn from the study before that assessment was carried out had this variable set to the last VAS pain score recorded prior to withdrawal. Other missing data were handled in the same way using the last available VAS pain score for that patient.

(6) The VAS pain score recorded 24 h after surgery. Patients that were withdrawn from the study before that assessment was carried out had this variable set to the last VAS pain score recorded prior to withdrawal. Other missing data were handled in the same way using the last available VAS pain score for that patient.

(7) The proportion of patients complaining of disturbed sleep due to pain at 10 a.m. on the morning following surgery. Patients that were withdrawn from the study prior to that had this variable set to 'complained of disturbed sleep'. Patients where no information has been recorded whether they complained of disturbed sleep or not were handled in the same way.

(8) The proportion of patients whose sensory block wore off within 2 h after surgery. Patients that were withdrawn from the study within 2 h of surgery whose sensory block did not wear off had this variable set to 'sensory block not worn off."

[Item 8, Vol. 1.90, p. 035 – 036]

Secondary efficacy variables were analysed only using the 'intent-to- treat' population in the following way:

a) "The time of first requirement for rescue analgesia (variable 1) was presented using Kaplan-Meier survival curves, displayed separately by extraction type and gender as well as combined. Separate analyses were performed for the 2 pairwise comparisons between the treatment groups (levobupivacaine vs lignocaine with adrenaline and levobupivacaine vs placebo) using the stratified log-rank test, adjusting for extraction type and gender."

b) "The proportion of patients requiring rescue analgesia within 48 h of surgery, the proportion of patients complaining of disturbed sleep due to pain at 10 a.m. on the morning following surgery and the proportion of patients whose sensory block wore off within 2 h after surgery (variables 2, 7 and 8) were analysed in an identical way to the primary efficacy variable (ie logistic regression). For the proportion of patients whose sensory block wore off within 2 h after surgery only extraction type and treatment were used as qualitative explanatory variables."

c) "The maximum VAS pain score recorded over the 2 h period after surgery, the time to maximum VAS pain score over the 2 h period after surgery and the VAS pain scores recorded 8 and 24 h after surgery (variables 3, 4, 5 and 6) were analysed using analysis of variance (ANOVA). Terms included in the model were extraction type, gender, treatment and an interaction between extraction type and treatment. If the interaction term was not significant at the 10% level it was dropped from the model."

"...ing the error variance from the ANOVA, pairwise comparisons between the treatment groups ...upivacaine via lignocaine with adrenaline and levobupivacaine vs placebo) were carried out using Student's 't' distribution. Estimates of the differences in the adjusted means between the treatment groups and the associated 95% confidence intervals were presented."

"The residuals from this analysis were submitted to a Shapiro-Wilk test for normality and examined graphically to assess variance homogeneity. Any deviation from either assumption entailed a re-analysis using an appropriate alternative transformation of the data (such as the logarithmic or power transformation). Furthermore, following examination of these data, non-parametric methods were used if the above methods were not considered appropriate."

Since 2 pairwise comparisons were performed for each of the secondary efficacy variables, the stepwise Bonferroni-Holm procedure with nominal levels of significance of α=0.025 and 0.05 was applied in order to ensure that the multiple level of significance for each of them was α=0.05. Using this procedure, the smaller p-value was compared against an α level of 0.025, and if significant the larger p-value was compared against an a' level of 0.05. No further adjustment was made for the number of secondary efficacy variables."

[Item 8, Vol. 1.90, p. 036 –038]

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 95 patients randomized, only 93 (7.9%) were eligible for the safety and the intent-to-treat populations – 32 in the placebo group, 31 in the lidocaine with epinephrine group and 30 in the levobupivacaine group. Two patients (Nos. 107 and 127) were withdrawn prior to receiving study medication. Patient 107 was withdrawn by the anesthesiologist and patient 127 was cancelled secondary to nasal congestion.

Four patients were considered major protocol violators and were excluded from the per-protocol population. Consequently, 89 patients (31 in the placebo group, 30 in the lidocaine with epinephrine group, and 28 in the levobupivacaine group) were in the per-protocol population.

Table 174. Patient Disposition

TABLE 3.1

Populations for Analysis
Patients in Each Population
Summary Statistics: All Patients

Treatment	Safety				Intent-to-Treat				Per-Protocol			
	YES		NO		YES		NO		YES		NO	
	N	%	N	%	N	%	N	%	N	%	N	%
PLACEBO	32	100.0	0	0	32	100.0	0	0	31	96.9	1	3.1
0.75% LEVOBUPIVACAINE	30	96.8	1	3.2	30	96.8	1	3.2	28	90.3	3	9.7
2% LIGNOCAINE WITH ADRENALINE	31	96.9	1	3.1	31	96.9	1	3.1	30	93.8	2	6.3
ALL	93	97.9	2	2.1	93	97.9	2	2.1	89	93.7	6	6.3

[Sponsor's Table 3.1, Item 8, Vol. 1.90, p. 069]

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Table 175. Patient – Specific Protocol Violations

TABLE 3.2

Populations for Analysis
Reason for Exclusion from Intent-to-Treat and Per-Protocol Population
By Treatment
Summary Statistics: All Patients

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
ALL PATIENTS	N	32	31	32	95
	%	100.0	100.0	100.0	100.0
STUDY MEDICATION (1)	N	0	1	1	2
	%	0	3.2	3.1	2.1
VALID FOR INTENT-TO-TREAT	N	32	30	31	93
	%	100.0	96.8	96.9	97.9
COMPLICATED SURGEY	N	1	2	1	4
	%	3.1	6.5	3.1	4.2
VALID FOR PER-PROTOCOL	N	31	28	30	89
	%	96.9	90.3	93.8	93.7

TABLE 3.3

Populations for Analysis
Reason for Exclusion from Intent-to-Treat and Per-Protocol Population
Individual Values: All Patients

Patient	Treatment	Age (Years)	Height (cm)	Weight (kg)	Valid for Per-Protocol Population	Valid for Intent-to-Treat Population	Reason for Exclusion
011	0.75% LEVOBUPIVACAINE	24	157	51	NO	YES	COMPLICATED SURGERY
044	2% LIGNOCAINE WITH ADRENALINE	27	169	64	NO	YES	COMPLICATED SURGERY
103	0.75% LEVOBUPIVACAINE	22	183	75	NO	YES	COMPLICATED SURGERY
107	0.75% LEVOBUPIVACAINE	22	.	.	NO	NO	DID NOT RECEIVE STUDY MEDICATION
127	2% LIGNOCAINE WITH ADRENALINE	21	156	60	NO	NO	DID NOT RECEIVE STUDY MEDICATION
135	PLACEBO	21	169	58	NO	YES	COMPLICATED SURGERY

[Sponsor's Table 3.2 and 3.3, Item 8, Vol. 1. 90 p. 070 and 071]

Demographics

The following table summarizes the demographic characteristics of the two treatment groups:

Table 176. Demographics -- Safety Population

TABLE 4.1.1

Demographic Details
By Treatment
Summary Statistics: Safety Population

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL
Age (Years)	Mean	25.5	24.9	23.7	24.7
	SD	4.7	5.1	3.7	4.5
	Min	18	18	18	18
	Max	39	41	32	41
	N	32	30	31	93
Height (cm)	Mean	168.4	164.3	164.5	165.8
	SD	9.0	7.8	8.8	8.7
	Min	148	145	148	145
	Max	183	183	183	183
	N	32	30	31	93
Weight (kg)	Mean	67.06	65.17	64.31	65.53
	SD	14.27	11.68	12.86	12.92
	Min	45.0	43.0	45.0	43.0
	Max	94.0	100.0	108.0	108.0
	N	32	30	31	93

[Sponsor's Table 4.1.1 , Item 8, Vol.1.90, p. 072]

Table 177. Demographics – Intent-to-Treat and Per-protocol Populations

TABLE 3.2

Populations for Analysis
Reason for Exclusion from Intent-to-Treat and Per-Protocol Population
By Treatment
Summary Statistics: All Patients

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
ALL PATIENTS	N	32	31	32	95
	%	100.0	100.0	100.0	100.0
STUDY MEDICATION (i)	N	0	1	1	2
	%	0	3.2	3.1	2.1
VALID FOR INTENT-TO-TREAT	N	32	30	31	93
	%	100.0	96.8	96.9	97.9
COMPLICATED SURGEY	N	1	2	1	4
	%	3.1	6.5	3.1	4.2
VALID FOR PER-PROTOCOL	N	31	28	30	89
	%	96.9	90.3	93.8	93.7

Intent-to-treat population excludes: (i) patients who did not receive study medication
Per-protocol population excludes: (iii) patients who received prohibited medication and patients in (i)
Note: Two patients were withdrawn prior to dosing

[Sponsor's Table 3.2., Item 8, Vol. 1.90, p. 070]

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ON ORIGINAL

Safety Population

A total of 93 patients were included in the safety population. This group had a mean age of 24.7 years (range 1841 years, SD = 4.5), mean height of 165.8cm (range 145-183cm, SD = 8.7) and mean weight of 65.53 kg (range 43.0-108.0 kg, SD = 12.92)."

"The levobupivacaine group had a mean age of 24.9 years (range 18-41 years, SD = 5.1), mean height of 164.3 cm (range 145-183 cm, SD = 7.8) and mean weight of 65.17 kg (range 43.0-100.0kg, SD = 11.68). The lignocaine with adrenaline group had a mean age of 23.7 years (range 18-32 years, SD = 3.7), mean height of 164.5 cm (range 148-183 cm, SD =8.8) and mean weight of 64.31 kg (range 45.0-108.0 kg, SD = 12.86). The placebo group had a mean age of 25.5 years (range 18-39 years, SD = 4.7), mean height of 168.4 cm (range 148-183cm, SD = 9.0) and mean weight of 67.06 kg (range 45.0-94.0 kg, SD = 14.27)."

Intent-to-Treat Population

"No patients from the 'safety' population were excluded from the 'intent-to-treat' population."

Per-Protocol Population

"A total of 89 patients of mean age 24.8 years (range 18-41 years, SD = 4.6) were included in the 'per-protocol' population. This group had a mean height of 165.6 cm (range 145-183 cm, SD = 8.6) and a mean weight of 65.69 kg (range 43.0-108.0 kg, SD = 13.05). The mean age of patients in the 'per-protocol' population was 25.1 years (range 18-41 years, SD = 5.2) for the levobupivacaine group, 23.6 years (range 18-32 years, SD = 3.7) for the lignocaine with adrenaline group and 25.6 years (range 18-39 years, SD = 4.7) for the placebo group."

"The mean height of this population was 163.9 cm (range 145-177 cm, SD =7.0), 164.3 cm (range 148-183 cm, SD = 8.9) and 168.4 cm (range148-183cm, SD = 9.1) for the levobupivacaine, lignocaine with adrenaline and placebo treated groups respectively."

"The 3 treatment groups were reasonably well balanced for age (using all 3 populations), but the range within the lignocaine with adrenaline group was narrower than for the other 2 groups with the maximum age being only 32. Height and weight was reasonably well balanced between the treatment groups. Race was well balanced between treatments except for the
fact that there were only 2 Asian patients in the levobupivacaine group compared to 6 in each of the other 2 treatment groups."

"Gender was not well balanced between treatments: there were similar numbers of male and female patients in the placebo group (17 and 15 respectively), but both the other treatment groups contained far fewer males than females. In the levobupivacaine group there were 8 males and 22 females, and in the lignocaine with adrenaline group there were only 4 males and 27 females. It should be noted that all analyses adjust for the imbalance in gender."

Historical or concomitant diseases were reported by 48 patients. The incidence of the various disease types was spread relatively evenly amongst the treatment groups. The most commonly reported medical condition was asthma, present in 18.3% of patients. Allergy to antibiotics was reported in 5.4% of patients."

"97.8% of patients in the safety population received medication for the musculoskeletal system, mainly analgesics. 93.5% of patients received general antinfectives for systemic use. These were mainly antibiotics given prophylactically."

[Item 8, Vol. 1.90 p. 045-049]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Variable

"The primary measure of efficacy was defined as the proportion of patients requiring rescue analgesia within 2 hours after the completion of surgery. "In the 'intent-to-treat' population just over half (53.3%) the patients on levobupivacaine requested rescue medication within 2 h of surgery completion whereas almost ¾ of patients on the other 2 treatments (71.0% in the lignocaine with adrenaline group and 71.9% in the placebo group) took rescue analgesia in the 2 h period after surgery. A similar pattern was observed in the per-protocol population (53.6%, 73.3% and 74.2% took rescue medication in the levobupivacaine, lignocaine with adrenaline and placebo groups respectively)."

"For the intent-to-treat population, the differences between the treatments were not statistically significant at the 5% level (p=0.078 and 0.21 for levobupivacaine vs placebo and levobupivacaine vs lignocaine with adrenaline respectively). The estimate (95% CI) of the odds ratio between levobupivacaine and placebo was 2.79 (0.89, 8.71) showing that the odds of requiring rescue analgesia within 2 h are almost 3 times higher for the placebo group compared to the levobupivacaine group. The estimate (95% CI) of the odds ratio between levobupivacaine and lignocaine with adrenaline was 2.00 (0.67, 5.94) showing that the odds of requiring rescue analgesia within 2 h are about twice as high for the placebo group as for the levobupivacaine group."

"The results in the per-protocol population were very similar (p=0.061 and 0.12 for levobupivacaine vs placebo and levobupivacaine vs lignocaine with adrenaline respectively). The estimate (95% CI) of the odds ratio between levobupivacaine and placebo was 3.15 (0.95,10.42) showing that the odds of requiring rescue analgesia within 2 h are about 3 times higher for the placebo group compared to the levobupivacaine group. The estimate (95% CI) of the odds ratio between levobupivacaine and lignocaine with adrenaline was 2.46 (0.78, 74) showing that the odds of requiring rescue analgesia within 2 h are about 2½ times higher for the lignocaine with adrenaline for the placebo group as the levobupivacaine group."

"The differences between the compared treatments were not found to be different for patients with unilateral and bilateral extractions, since the treatment by extraction type interaction term was not found significant at the 10% significance level (p=0.76 and 0.80 for intent-to-treat and per-protocol populations respectively). It was therefore excluded from the model for both populations."

The statistical reviewer tested for the relative risk using the Fisher Exact test and found similar results, i.e., no statistical significance between the two treatment groups.

[Item 8, Vol. 1.90, p. 049 –050]

Proportion of Patients Requiring Rescue Analgesia Within 48 h of Surgery

"Values for this secondary efficacy variable were very similar for the 3 treatment groups because only one patient in the trial did not take rescue medication within 48 h of the operation. This patient was randomised to levobupivacaine."

"Due to a large number of empty cells, the logistic regression analysis was no longer applicable, and Fisher's exact test was used instead. The 2 separate treatment comparisons were analysed in two 2 x 2 contingency tables, without taking the explanatory variables extraction type and gender into account. It was also not possible to test the consistency of the treatment differences across extraction types."

"The difference between levobupivacaine and placebo was not found to be statistically significant at the 5% level (p=0.48). The difference between levobupivacaine and lignocaine with adrenaline was also not found to be statistically significant at the 5% level (p=0.49)."

Maximum VAS Pain Score Over the 2 h Period After Surgery

"The means for the maximum VAS pain score over the 2 h period after surgery from the ANOVA (adjusted for extraction type and gender) were 40.30, 47.75 and 52.83 for the levobupivacaine, lignocaine with adrenaline and placebo treatment groups respectively. The difference between levobupivacaine and lignocaine was not statistically significant at the 5% level (p=0.24). The estimate (95% CI) of the difference between levobupivacaine and lignocaine with adrenaline was -7.45 (-9.81, 4.92), showing that the maximum pain values for the levobupivacaine group were on average 7.45 mm (measured on a 100 mm visual analogue scale) lower than for the lignocaine with adrenaline group. Using the stepwise Bonferroni-Holm procedure, the difference between levobupivacaine and placebo was also not statistically significant (p=0.050) as the p-value was greater than 0.025. The estimate (95% CI) of the difference between levobupivacaine and placebo was -12.54 (-25.08, 0.01), showing that the maximum pain values for the levobupivacaine group were on average 12.54 mm (measured on a 100 mm visual analogue scale) lower than for the placebo group."

"The differences between the compared treatments were not found to be different across extraction types. The treatment by extraction type interaction term was found not significant at the 10% significance level (p=0.41) and was therefore excluded from the model."

"Generally, gender and extraction type were not found to significantly influence the maximum pain scores. The assumptions of normality and homogeneity of variances were satisfied."

The statistical reviewer confirms this finding, i.e., the treatment difference is not statistically significant.

[Item 8, Vol. 1.90, p. 052 –053]

Time to Maximum VAS Pain score Over the 2 h Period After Surgery

"The assumption of normality was not satisfied for the time to maximum VAS pain score over the 2 h period after surgery. This was because time to maximum pain was essentially a categorical variable, with the majority of patients in the 30 min category, which caused skewness. There are problems with power transformations when confidence intervals are calculated for the difference between treatment groups (on the original scale confidence intervals for the difference between treatment groups are not consistent with the means in each treatment group). Therefore a non-parametric analysis was carried out instead."

"The median for time to maximum VAS pain scores was 37 min in both the placebo and levobupivacaine treatment groups and 35 min in the lignocaine group. Differences between the treatment groups were not statistically significant at the 5% level (p=0.59 and 0.15 for levobupivacaine vs placebo and levobupivacaine vs lignocaine with adrenaline respectively). The estimate of the median difference between with adrenaline levobupivacaine and placebo (95% CI) was 0 min (-5,15) min. The estimate of the median difference between levobupivacaine and lignocaine with adrenaline (95% CI) was 0 min (-6,15) min".

"The treatment by extraction type interaction term was found to be significant at the 10% significance level (p=0.019) and was therefore included in the model. In the unilateral group, maximum pain was reached quickest on levobupivacaine and then placebo, whereas the bilateral group felt pain soonest on lignocaine with adrenaline and then placebo."

"Generally, gender was not found to significantly influence the time to maximum pain. Extraction type was found to significantly influence the time to maximum pain: the ranks for patients with unilateral surgery were higher than those for patients with bilateral surgery showing that, generally, time to maximum pain was greater for patients in the unilateral surgery group."

[Item 8, Vol. 1.90, p. 053 –056]

VAS Pain Score Recorded 8 h After Surgery

The means for the VAS pain score 8 h after surgery from the ANOVA (adjusted for extraction type and gender) were 29.62, 32.35 and 42.93 for the levobupivacaine, lignocaine with adrenaline and placebo treatment groups respectively. The difference between levobupivacaine and lignocaine with adrenaline was not statistically significant at the 5% level (p=0.71). The estimate (95% CI) of the difference between levobupivacaine and lignocaine with adrenaline was -2.73 (-17.30,11.84), showing that the pain values for the levobupivacaine group were on average 2.73 mm (measured on a 100 mm visual analogue scale) lower than for the lignocaine with adrenaline group. The difference between levobupivacaine and placebo was not statistically significant at the 5% level (p=0.077). The estimate (95% CI) of the difference between levobupivacaine and placebo was -13.32 (-28.13,1.49), showing that the pain values for the levobupivacaine group were on average 13.32 mm (measured on a 100 mm visual analogue scale) lower than for the placebo group."

"The differences between the compared treatments were not found to be consistent across extraction types. The treatment by extraction type interaction term was found to be statistically significant at the 10% significance level (p=0.013) and was therefore included in the model. In the unilateral group, people on placebo gave the highest pain scores whereas the other 2 treatment group mean scores were much lower, but very similar to each other. In the bilateral surgery group, the lowest pain scores came from the placebo recipients and the highest from the patients on lignocaine."

"Generally, gender was not found to significantly influence the maximum pain scores. Although the treatment by extraction type interaction term was found to be significant, neither the treatment nor the extraction type effects were found to significantly influence the VAS pain score 8 h after surgery. The assumptions of normality and homogeneity of variances were satisfied."

[Item 8, Vol. 1.90, p. 055 –056]

AS Pain score Recorded 24 h After Surgery

"The means for the VAS pain score 24 h after surgery from the ANOVA (adjusted for extraction type and gender) were 24.63, 23.26 and 36.47 for the levobupivacaine, lignocaine with adrenaline and placebo treatment groups respectively. The difference between levobupivacaine and lignocaine with adrenaline was not statistically significant at the 5% level (p=0.85). The estimate (95% CI) of the difference between levobupivacaine and lignocaine with adrenaline was 1.37 (-13.16, 15.90), showing that the pain values for the levobupivacaine group were on average 1.37 mm (measured on a 100 mm visual analogue scale) higher than for the lignocaine with adrenaline group. The difference between levobupivacaine and placebo was not statistically significant at the 5% level (p=0.12). The estimate (95% CI) of the difference between levobupivacaine and placebo was -11.84 (-26.61, 2.93), showing that the pain values for the levobupivacaine group were on average 11.84 mm (measured on a 100 mm visual analogue scale) lower than for the placebo group."

"The differences between the compared treatments were not found to be consistent across extraction types. The treatment by extraction type interaction term was found to be statistically significant at the 10% significance level (p=0.01 1) and was therefore included in the model.
The interaction pattern for this variable is very similar to the VAS pain score at 8 h, except that for patients in the unilateral surgery group, the lignocaine pain score is slightly lower than that for the other 2 treatment groups."

"Generally, gender was not found to significantly influence the maximum pain scores. Although the treatment by extraction type interaction term was found to be significant, neither the treatment nor the extraction type effects were found to significantly influence the VAS pain score 24 h after surgery. The assumptions of normality and homogeneity of variances were satisfied."

[Item 8, Vol. 1.90, p. 056 –057]

Proportion of Patients Complaining of Disturbed Sleep Due to Pain at 10 a.m. on the Morning ollowing Surgery

"Less patients in the placebo group had trouble with sleep due to pain (46.9%) than those on levobupivacaine and lignocaine with adrenaline (70.0% and 77.4% respectively)."

"The differences between the treatments were not statistically significant at the 5% level (p=0.12 and 0.64 for levobupivacaine vs placebo and levobupivacaine vs lignocaine with adrenaline respectively). The estimate (95% CI) of the odds ratio between levobupivacaine and placebo was 2.48 (0.79, 7.76) showing that the odds of complaining of disturbed sleep are about 21A times higher for the levobupivacaine group compared to the placebo group. The estimate (95% CI) of the odds ratio between levobupivacaine and lignocaine with adrenaline was 0.74 (0.22, 2.55) showing that the odds of complaining of disturbed sleep are almost 1 ½ times higher for the lignocaine with adrenaline group compared to the levobupivacaine group."

"The differences between the compared treatments were not found to be different for the different extraction types. The treatment by extraction type interaction term was not found significant at the 10% significance level (p=0.86) and was therefore excluded from the model."

Proportion of Patients Whose Sensory Block Wore Off Within 2 h After Surgery

"Patient 157 had a missing value for this variable, so it was set to sensory block did not wear off, as a conservative approach and in order to be consistent with the other efficacy variables."

"In the placebo group, sensory block wore off within 2 h for 84.4% of patients whereas the corresponding figures for levobupivacaine and lignocaine with adrenaline were 6.7% and 3.2% respectively."

,he difference between levobupivacaine and placebo was statistically significant at the 5% level (p<0.001), but the difference between levobupivacaine and lignocaine with adrenaline was not statistically significant at the 5% level (p=0.54). The estimate (95% CI) of the odds
ratio between levobupivacaine and placebo was 0.01 (0.00, 0.07) showing that the odds of sensory block wearing off is one hundred times higher for the placebo group compared to the levobupivacaine group. The estimate (95% CI) of the odds ratio between levobupivacaine
and lignocaine with adrenaline was 2.15 (0.18, 25.14) showing that the odds of sensory block wearing off is more than twice as high for the levobupivacaine group as for the lignocaine with adrenaline group."

"The treatment by extraction type interaction could not be examined due to some empty cells in the contingency table and was therefore not included in the model. Generally, extraction type was not found to influence the proportion of patients whose sensory block wore off."

[Item 8, Vol. 1.90, p. 057 –059]

Table 178. Analysis of Primary Efficacy Variable – Requirement for Rescue Medication

TABLE 7.1

Patients Requiring Rescue Medication Within 2 Hours of Surgery
Summary Statistics: Intent-to-Treat Population

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
YES	N	23	16	22	61
	%	71.9	53.3	71.0	65.6
NO	N	9	14	9	32
	%	28.1	46.7	29.0	34.4
ALL	N	32	30	31	93
	%	100.0	100.0	100.0	100.0

Table 179. Analysis of Secondary Variable – Time to First Rescue Medication

TABLE 8.1

Time to First Requirement For Rescue Analgesia (minutes)
Summary Statistics: Intent-to-Treat Population

	PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
Mean	93.3	257.6	85.9	143.9
SD	112.4	538.5	94.0	323.7
Median	45.0	87.5	55.0	55.0
Min	5	20	5	5
Max	479	2880	445	2880
N	32	30	31	93

Sponsor's Table 7.1 and 8.1, Item 8, Vol. 1.90, p. 088 and 090]

Table 180. Analysis of Secondary Efficacy Variable – Post – Operative Rescue Mediation

TABLE 8.2

Patients Requiring Rescue Medication Within 48 Hours of Surgery
Summary Statistics: Intent-to-Treat Population

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
YES	N	32	29	31	92
	%	100.0	96.7	100.0	98.9
NO	N	0	1	0	1
	%	0	3.3	0	1.1
ALL	N	32	30	31	93
	%	100.0	100.0	100.0	100.0

Table 181. Analysis of Secondary Efficacy Variable – Maximum Pain Score

TABLE 9.1.1

Maximum Pain Score (mm) Recorded Within 2 Hours of Surgery
Statistical Analysis: Intent-to-Treat Population

Treatment	Means [1]	Comparison	
		Difference[2] (95% CI)	Significance[3]
LEVOBUPIVACAINE	40.30	-	-
LIGNOCAINE	47.75	-7.45 (-19.81, 4.92)	0.24
PLACEBO	52.83	-12.54 (-25.08, 0.01)	0.050[4]

Results obtained from parametric analysis of variance of maximum VAS pain score, including terms for extraction type (p=0.12), gender (p=0.14) and treatment (p=0.14).
Data used in analysis are listed in Data Listing 10.2.
VAS Scale: 0 = no pain, 100 = worst pain.

1 Represents adjusted arithmetic means from ANOVA.
2 Represents difference from levobupivacaine.
3 p-value for comparison using error variance from ANOVA with Student's t distribution.
4 Even though p=0.050 this comparison is not significant at the 5% significance level due to the use of the Bonferroni-Holm adjustment for multiple comparisons.

[Sponsor's Table 8.2 and 9. 1 .1, Item 8, Vol. 1.90, p. 091 and 092]

Table 182. Analysis of Secondary Outcome Measurement

Post-Operative Time to Maximum Pain Score

TABLE 9.1.2

Time to Maximum Pain Score Recorded Over the 2 Hour Period After Surgery (minutes)
Statistical Analysis: Intent-to-Treat Population

Treatment	Medians			Comparison	
	Unilateral (n=15)	Bilateral (n=78)	Overall (n=93)	Difference[1] (95% CI)	Significance
LEVOBUPIVACAINE	35 (n=5)	40 (n=25)	37 (n=30)	-	-
LIGNOCAINE	120 (n=5)	30 (n=26)	35 (n=31)	0 (-6, 15)	0.15
PLACEBO	70 (n=5)	35 (n=27)	37 (n=32)	0 (-5, 15)	0.59

Results obtained from Generalised Wilcoxon Test (analysis of variance of ranked time to maximum VAS pain score), including terms for extraction type (p=0.003), gender (p=0.083), treatment (p=0.48) and extraction type by treatment interaction (p=0.019).
Data used in analysis are listed in Data Listing 10.2.

[1] Represents overall difference from levobupivacaine.

Table 183. Analysis of Secondary Outcome Measurement – 8 Hour Post-Operative VAS Score

TABLE 9.1.3

VAS Pain Score (mm) Recorded 8 Hours After Surgery
Statistical Analysis: Intent-to-Treat Population

Treatment	Means [1]			Comparison	
	Unilateral (n=15)	Bilateral (n=78)	Overall (n=93)	Difference[2] (95% CI)	Significance[3]
LEVOBUPIVACAINE	22.83 (n=5)	36.41 (n=25)	29.62 (n=30)	-	-
LIGNOCAINE	23.98 (n=5)	40.72 (n=26)	32.35 (n=31)	-2.73 (-17.30, 11.84)	0.71
PLACEBO	54.32 (n=5)	31.54 (n=27)	42.93 (n=32)	-13.32 (-28.13, 1.49)	0.077

Results obtained from parametric analysis of variance of VAS pain score, including terms for extraction type (p=0.69), gender (p=0.16), treatment (p=0.73) and extraction type by treatment interaction (p=0.013).
Data used in analysis are listed in Data Listing 10.2.
VAS Scale: 0 = no pain, 100 = worst pain.

[1] Represents adjusted arithmetic means from ANOVA.
[2] Represents overall difference from levobupivacaine.
[3] p-value for overall comparison using error variance from ANOVA with Student's t distribution.

[Sponsor's Table 9. 1. 2 and 9. 1. 3, Item 8, Vol. 1.90, p. 093 and 094]

Table 184. Analysis of Secondary Outcome Measurement – 24 Hour Post-Operative VAS Score

TABLE 9.1.4

VAS Pain Score (mm) Recorded 24 Hours After Surgery
Statistical Analysis: Intent-to-Treat Population

Treatment	Means [1]			Comparison	
	Unilateral (n=15)	Bilateral (n=78)	Overall (n=93)	Difference[2] (95% CI)	Significance[3]
LEVOBUPIVACAINE	15.62 (n=5)	33.65 (n=25)	24.63 (n=30)	-	-
LIGNOCAINE	10.63 (n=5)	35.90 (n=26)	23.26 (n=31)	1.37 (-13.16, 15.90)	0.85
PLACEBO	44.79 (n=5)	28.15 (n=27)	36.47 (n=32)	-11.84 (-26.61, 2.93)	0.12

Results obtained from parametric analysis of variance of VAS pain score, including terms for extraction type (p=0.14), gender (p=0.053), treatment (p=0.95) and extraction type by treatment interaction (p=0.011).
Data used in analysis are listed in Data Listing 10.2.
VAS Scale: 0 = no pain, 100 = worst pain.

1 Represents adjusted arithmetic means from ANOVA.
2 Represents overall difference from levobupivacaine.
3 p-value for overall comparison using error variance from ANOVA with Student's t distribution.

Table 185. Analysis of Secondary Outcome Measurement – Patient Complaints of Disturbed Sleep at 10 am

TABLE 10

Patients Complaining of Disturbed Sleep At 10 am On The Morning Following Surgery
Summary Statistics: Intent-to-Treat Population

Sleep Disturbed By Pain		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
NO	N	17	9	7	33
	%	53.1	30.0	22.6	35.5
YES	N	15	21	24	60
	%	46.9	70.0	77.4	64.5
ALL	N	32	30	31	93
	%	100.0	100.0	100.0	100.0

[Sponsor's Tables 9. 1. 4 and 10, Item 8, Vol. 1.90, p. 095 and 100]

Table 186. Analysis of Secondary Outcome Measurement –

Patient Lip Still Numb 2 Hours Post Operation

TABLE 11.1

Patients Lip Still Numb Within 2 Hours of Surgery
Summary Statistics: Intent-to-Treat Population

		PLACEBO	0.75% LEVOBUPIVACAINE	2% LIGNOCAINE WITH ADRENALINE	ALL PATIENTS
YES	N	5	28	30	63
	%	15.6	93.3	96.8	67.7
NO	N	27	2	1	30
	%	84.4	6.7	3.2	32.3
ALL	N	32	30	31	93
	%	100.0	100.0	100.0	100.0

[Sponsor's Table 11.1, Item 8, Vol. 1.90, p. 101]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable was median time to first requirement of rescue analgesia. The differences between the treatments were not statistically significant at the 5% level (p=0.045 and p=0.062 for levobupivacaine vs. lidocaine with epinephrine and levobupivacaine vs. placebo).

The analysis of secondary variables similarly revealed no statistical significance at the 5% level.

The treatment by extraction type interaction term was found to be significant at the 10% significance level (p=0.019), i.e., in the unilateral group, maximum pain was reached quickest on levobupivacaine and then placebo, whereas the bilateral group felt pain soonest on lidocaine with epinephrine and then placebo. Additionally, the unilateral placebo group gave the highest pain scores whereas the other 2 treatment group mean scores were much lower, but very similar to each other. In the bilateral surgery group, the lowest pain scores came from the placebo recipients and the highest from the patients on lidocaine (p=0.013).

The clinical data provided no statistical difference between levobupivacaine's vs. bupivacaine's ability to provide a superior inferior alveolar nerve block for post-operative dental pain. However, clearly the product was effective in providing anesthesia for dental surgery.

STUDY # CS-007

PROTOCOL SYNOPSIS:

Title: "Double-blind Randomised, Controlled Trial of 0.5% Levobupivacaine for Post-operative Pain Control in Paediatric Patients Following Hernia Repair Surgery"

Primary Objective: "To assess the efficacy of levobupivacaine to provide adequate post-operative pain control"

Secondary Objective: To assess the, (1) analgesia produced, (2) time to first rescue medication, (3) overall quality of block, and to evaluate the safety profile of 0.5% levobupivacaine

[Item 8, Vol. 1.92, p. 018]

Study Design:

The study is designed as a single center, randomized, double-blind, parallel group study of the efficacy and safety of 0.5% levobupivacaine to provide adequate post-operative pain control in pediatric patients (ages 6 months to 12 years) undergoing unilateral or bilateral herniorrhaphy. Patients received either an ilioinguinal-iliohypogastric (IIIH) nerve block using 0.5% levobupivacaine (0.25 ml/kg) or no block. The protocol calls for two groups of twenty patients to each be randomly assigned on a 1:1 ratio to one of two treatment arms.

Group I 0.5% levobupivacaine
Group II No Block

Eligible patients were ASA Class I or III males or females between 6 months and 12 years of age whose parent or guardian consented for an ilioinguinal-iliohypogastric nerve block for unilateral or bilateral herniorrhaphy. Patients had no prior history of systemic illness, allergies to amide local anesthetics, morphine, NSAIDS, acetaminophen, atropine or metoclopramide, or participation a clinical trial in previous month.

Eligible patients underwent a brief screening phase followed a fast according to standard hospital procedures. Prior to surgery, all patients received oral acetaminophen (15 mg/kg p.o.) 20-30 min before induction and metoclopramide 0.2 mg/kg as emesis prophylaxis. Atropine was also administered to all patients less than one year of age.

Induction of anesthesia was performed using sevoflurane in nitrous oxide and oxygen (2:1 ratio) in the induction room prior to transport to the operating room. Anesthesia was maintained with halothane in nitrous oxide and oxygen (2:1) via face mask or laryngeal mask airway. Unilateral or bilateral herniorrhaphy was then performed according to standard surgical practice.

Post-operatively, those patients randomized to receive a nerve block were administered 0.5% levobupivacaine in a IIIH nerve block and a Band-Aid at the puncture site (Time 0). Those patients randomized to receive no block received the Band-Aid at the puncture site only. All patients were then transferred to the post-anesthesia care unit (PACU) and monitored until complete resolution of the block.

Administration of the Ilioinguinal-Iliohypogastric (IIIH) Nerve Block

The ilioinguinal-iliohypogastric nerve block was carried out using 0.5% levobupivacaine in a dose of 0.25 ml/kg per operated side. A 22G 4 cm short bevel hypodermic needle was inserted 0.5-2.0 cm medial and superior to the anterior superior iliac spine (ASIS). Initially it was directed laterally and slightly inferiorly until it contacted the medial surface of the ASIS, at which point it was withdrawn a few millimeters and one-fourth of the study drug was injected following a negative aspiration test. The needle was then directed medially until a loss of resistance was felt upon piercing the aponeurosis of the anterior oblique muscle (i.e., Scarpa's fascia). The remaining study drug was deposited (following negative aspiration tests) in multiple locations below Scarpa's fascia in a fan-like pattern between the ASIS and the pubic tubercle.

Efficacy was assessed using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scale. It is as follows:

CHEOPS Scale:

Cry Codes:	Facial Codes:	Verbal Codes:	Torso Codes:	Touch Codes:	Legs Codes:
1 = No cry	1 = Composed	1 = None	1 = Neutral	1 = Not touching	1 = Neutral
2 = Moaning	2 = Grimace	1 = Other complaints	2 = Shifting	2 = Reach	2 = Squirming/kicking
2 = Crying	0 = Smiling	2 = Pain complaints	2 = Tense	2 = Touch	2 = Drawn up/tensed
3 = Scream		2 = Both complaints	2 = Shivering	2 = Grab	2 = Standing
		0 = Positive	2 = Upright	2 = Restrained	2 = Restrained
			2 = Restrained		

["CHEOPS Scale" Item 8,, Vol. 1.92, p. 128]

Using the CHEOPS scale, patients' pain was assessed at Time 0, then every 5-30 min, and finally every 15-min until the end of the two-hour period observation period. If the CHEOPS score was ≥ 10 the patient received rescue medication consisting of morphine 0.05 mg/kg iv at five minute intervals to a maximum of 1 mg/kg. If analgesia remained inadequate, ketorolac 1 mg/kg was administered once. If, at this point, the patient's pain was still not controlled, the patient was withdrawn from the study and treated.

Additionally, at the end of the two hour period, a blinded research nurse or sub-investigator, rated the overall quality of the block using the following scale: 0 = poor, 1 = fair, 2 = good, 3 = excellent.

Table 187. Schedule of Assessments

8.2 Patient Evaluation Schedule

Table 1 presents the patient evaluation schedule for this study.

Table 1 Patient Evaluation Schedule

Study Parameter	Pre-Study	Pre-Surgery	Surgery	Post-Surgery
Medical History and Informed Consent	X			
Physical Exam[1]	X			
Cardiovascular Monitoring (vital signs)	X		X	Every 30 minutes during the 2-hour observation period
Study Medication			X	
Pain Assessments (CHEOPS)				Time 0[2], every 5 minutes for 30 minutes, then every 15 minutes until the two-hour post-observation period is completed
Overall Assessment: Quality of the Block				X
Adverse Events	X	X	X	X[3]

[1]Includes body weight and height. [2]Time of Band-Aid(s) application. [3]Within 48 to 72 hours post-hospital discharge to determine residual effects of the study drug.

[Sponsor's Table 8.2, Item 8, Vol. 1.92, p. 029]

STATISTICAL ANALYSIS

The analysis of efficacy was performed on an intent-to-treat (ITT) population. The ITT population was defined as all randomized patients, excluding patients who did not receive the randomized treatment and patients who did not have any efficacy evaluations after the randomized treatment."

"All patients who were randomized were included in the population evaluated for safety. Since every patient who received the randomized treatment also had post-treatment efficacy evaluations, the ITT and safety population were identical."

All comparisons were done using a two-sided test with an alpha level of 0.05. Except where otherwise stated, all efficacy analyses were done on the Intent-to-Treat population."

"The primary parameter was the proportion of patients needing rescue analgesia, i.e., CHEOPS score equal to or greater than 10, in the two-hour post-operative observation period."

"The proportion of patients needing rescue analgesia was analyzed using Fisher's Exact test or chi-square test, as appropriate. Due to the small sample sizes, the Fisher Exact test was selected. If appropriate, a logistic regression was to be used to compare treatment with appropriate covariates (e.g., sex, type of surgery, time in surgery). A supportive analysis, utilizing the per-protocol population, is presented."

"The secondary parameters were the CHEOPS scores at various time points, the overall assessment of the quality of the block, the use of morphine and ketorolac, and time to first use of rescue medication."

"The CHEOPS scores at each time point, area under the curve minus baseline (AUCMB), and the overall assessment of the quality of the block were analyzed by a one-way analysis of variance (ANOVA) with treatment the independent variable. A 95% confidence interval for the mean difference is also presented. If appropriate, transformation (e.g., arcsine), logistic regression, or non-parametric statistic was to be used. The dichotomous parameters, usage of
morphine and ketorolac, were analyzed using a Fisher's Exact test or chi-square test, as appropriate. Due to the small sample sizes, the Fisher Exact test was selected. A survival analysis using the product-limit (Kaplan-Meier) approach with study drug as a treatment factor was used to analyze onset of time to first use of rescue medication."

[Item 8, Vol. 1.92, p. 033 –034]

"Several changes and clarifications to the planned statistical methods, were made on December 4, 1997, prior to the unblinding of the study. For the analysis of CHEOPS at each time point, the windowing rule was used to determine if the total CHEOPS would be used.

"Two computations, similar to Area Under the Curve Minus Baseline (AUCMB), normalized by time, were made. Both used a trapezoidal rule which weighted the average of any two successive observations by the length of time between them. The final sum was divided by the total time used, then the baseline was subtracted out."

$$CHEOPS\ AUCMB\ to\ rescue = \frac{\sum_{i=1}^{m}(t_i - t_{i-1})\frac{X_i + X_{i-1}}{2}}{t_m - t_0} - X_0$$

where t_0 = 0, time of Band-Aid placement,.
X_0 = 6 (empirically the minimum CHEOPS - see below),
t_i = the time at the i^{th} CHEOPS observation,
X_i = the i^{th} CHEOPS, and
m = the final CHEOPS observation at rescue or final observation, if no rescue

$$CHEOPS\ AUCMB\ to\ end = \frac{\sum_{i=1}^{m}(t_i - t_{i-1})\frac{X_i + X_{i-1}}{2}}{t_m - t_0} - X_0$$

where t_0 = 0, time of Band-Aid placement,
X_0 = 6 (empirically the minimum CHEOPS - see below),
t_i = the time at the i^{th} CHEOPS observation,
X_i = the i^{th} CHEOPS, and
m - the final (e.g., 2-hour) observation.

[Item 8, Vol. 1.92, p. 035]

"For both computations, if a CHEOPS observation preceded Time 0 (e.g., an observation at time -1 minute), it s ignored. Two patients (Patients Nos. 103 and 104) had negative relative times. In both cases, the ratings ..ere not done because the child was in the OR. When queried, the investigator indicated that the discrepancy was due to the use of different clocks for Time 0 and the first (missing) CHEOPS rating."

"Baseline CHEOPS and Change From Baseline: It was observed that 1) all non-missing CHEOPS before 10 minutes were always six, and 2) the first non-missing CHEOPS was always six. Therefore, the baseline was always six, a constant. It also follows that the two treatment's baseline means would also be equivalent to each other (and six). However, six is not the minimum CHEOPS, due to the possibility of ratings of zero for facial (smiling) or verbal (positive) ratings."

"For aesthetic reasons, we subtracted the baseline (6) in all CHEOPS presentations. The shift from analysis of the raw to the analysis of change from baseline had no affect on either the confidence interval of the difference between the two treatments or any inferential statistics. Negative change from baseline CHEOPS or AUCMB indicates a lower score than baseline and would be due to these smiling facial and/or positive verbal ratings."

"The CHEOPS change from baseline over time presentation is presented in two ways: 1) raw results, and 2) extending the CHEOPS at or immediately prior to taking rescue. It was realized, after unblinding the study, that using morphine would be expected to decrease the child's pain rating. We felt that without morphine or ketorolac the pain would likely remain unchanged over the two-hour study time period. Therefore, as a supplementary analysis, if a patient used morphine (rescue), we would use the patient's pain rating at the time the first rescue was administered or the rating immediately prior to the first rescue, whichever came last."

[Item 8, Vol. 1.92, p. 035 –036]

PROTOCOL AMENDMENT:

Amendment 1 dated 4/7/97 made the following changes:

A. Follow -up

- The wording has been revised to give specific examples of follow-up questions to be asked as well as the administrative plan for the responses received

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 38 patients randomized, three patients were withdrawn prior to receiving study drug, leaving 35 patients (83.3%) being eligible for the safety population. These same 35 patients (100%) received one post – efficacy evaluation and therefore were eligible for the Intent-to-Treat population. There were two patients, however, who represented protocol violations, leaving the number of per-protocol population members at 33 (72.2%).

Specifically, Patient 111 was withdrawn received a local block by the surgeon, Patient 119 received an umbilical hernia repair in addition to the scheduled hemiorrhaphy, and Patient 122 required dissection of large hydroceles. These were the only patients withdrawn prior to receiving randomized drug.

There were two patients who exceeded the upper age limit but who were given exemptions to be included in the study.

Table 188. Patient Disposition

TABLE 1

PATIENT DISPOSITION (1) BY TYPE OF SURGERY

NUMBER OF PATIENTS	0.5% LEVOBUPIVACAINE W/ CO			NO BLOCK W/ CO		
	UNILATERAL	BILATERAL	OVERALL	UNILATERAL	BILATERAL	OVERALL
RANDOMIZED	15 (100.0%)	5 (100.0%)	20 (100.0%)	13 (100.0%)	5 (100.0%)	18 (100.0%)
WITHDREW PRIOR TO RECEIVING RANDOMIZED TREATMENT	0	0	0	1 (7.7%)	2 (40.0%)	3 (16.7%)
RECEIVED RANDOMIZED TREATMENT (SAFETY POPULATION)	15 (100.0%)	5 (100.0%)	20 (100.0%)	12 (92.3%)	3 (60.0%)	15 (83.3%)
RECEIVED RANDOMIZED TREATMENT WITH POST-EFFICACY EVALUATION (ITT POPULATION)	15 (100.0%)	5 (100.0%)	20 (100.0%)	12 (92.3%)	3 (60.0%)	15 (83.3%)
PER-PROTOCOL-EVALUABLE	15 (100.0%)	5 (100.0%)	20 (100.0%)	12 (92.3%)	1 (20.0%)	13 (72.2%)
NON-PROTOCOL-EVALUABLE	0	0	0	0	2 (40.0%)	2 (11.1%)
DISCONTINUED	0	0	0	1 (7.7%)	2 (40.0%)	3 (16.7%)
COMPLETED	15 (100.0%)	5 (100.0%)	20 (100.0%)	12 (92.3%)	3 (60.0%)	15 (83.3%)

[Sponsor's Table 1, Item 8, Vol. 1.92, p. 259]

APPEARS THIS WAY
ON ORIGINAL

Table 189. Patient – Specific Protocol Violations

PATIENT NUMBER/CENTER	TREATMENT GROUP	VIOLATION	PATIENT TOTALS N (%)
			38 (100) Randomized
Excluded from Safety Population:			
111,	Not Treated	Local block administered by surgeon	35 (83.3) Safety Population
119,		Received Umbilical Hernia Repair	
122		Received Hydrocele Resection[16]	
Excluded from Intent-to-Treat:			
None			35 (83.3) Intent-to-Treat
Excluded from Per-Protocol:			
Two (Patient numbers not specified)	Not Specified	Age Exceeded Upper Limits	33 (72.2) Per-Protocol
3 (16.7%)Total Withdrawal			**35 (83.3%) Total Completed**

[16] Extensive resection involved which was considered to likely be more painful than hemiorrhaphy.

Table 190. Study Termination

TABLE 2

STUDY TERMINATION (1)

	0.5% LEVOBUPIVACAINE II (2)			0.5% BUPIVACAINE II (2)		
	UNILATERAL	BILATERAL	OVERALL	UNILATERAL	BILATERAL	OVERALL
RANDOMIZED	15 (100.0%)	5 (100.0%)	20 (100.0%)	13 (100.0%)	5 (100.0%)	18 (100.0%)
RANDOMIZED, BUT DID NOT RECEIVE RANDOMIZED STUDY DRUG	0	0	0	NA	NA	NA
COMPLETED	15 (100.0%)	5 (100.0%)	20 (100.0%)	12 (92.3%)	3 (60.0%)	15 (83.3%)
TERMINATED PREMATURELY	0	0	0	1 (7.7%)	2 (40.0%)	3 (16.7%)
REASON FOR TERMINATION						
ADVERSE EVENT	0	0	0	0	0	0
PATIENT'S PARENT OR GUARDIAN REQUEST	0	0	0	0	0	0
NON-COMPLIANCE	0	0	0	0	0	0
INTERCURRENT ILLNESS	0	0	0	0	0	0
INVESTIGATOR JUDGEMENT	0	0	0	0	1/ 2 (50.0%)	1/ 3 (33.3%)
TERMINATED BY SPONSOR	0	0	0	0	0	0
LOST TO FOLLOW-UP	0	0	0	0	0	0
PROTOCOL VIOLATION	0	0	0	1/ 1 (100.0%)	1/ 2 (50.0%)	2/ 3 (66.7%)
UNAUTHORIZED CHANGE IN TREATMENT	0	0	0	0	0	0
UNABLE TO CONTROL POST-OP PAIN	0	0	0	0	0	0
DEATH	0	0	0	0	0	0
OTHER	0	0	0	0	0	0

(1) Percentages for reason for termination are based on number of patients terminated prematurely; other percentages are based on number of randomized patients.

PROJECT16:[CHIRO5905.TABLES]T02.SAS 17:05 December 22, 1997

Reference: LISTING 14

[Sponsor's Table 2, Item 8, Vol. 1.92, p. 260]